69. The method of claim 66, wherein the immunoassay is a competitive immunoassay.

70. The method of claim 66, wherein the immunological binding partner is an antibody. --

REMARKS

Applicants have carefully reviewed the Office Action dated December 9, 1997, and submit the amendments above and the remarks to follow as a full and complete response thereto.

Claims 1-38 are currently pending. Of these claims, claims 1-30 are the only claims to have been examined on the merits, due to a restriction requirement. In this Response, applicants cancel claims 1-38, and replace the subject matter of claims 1-30 with new claims 39-70. Therefore, claims 39-70 are presented for reconsideration.

The Office Action states that the amendments to claims 8, 12 and 21 were not entered due to the inconsistency between the claim language and the amendment.

These claims have been cancelled, therefore this issue is now moot.

Claims 27-30 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Claims 27-30 have been cancelled, and new claims 66-70 are based thereon. Applicants submit that new claims 66-70 are in full compliance with 35 U.S.C. § 112, second paragraph.

Claims 1, 3, 5-7, 9, 11-13 and 15-17 are rejected under 35 U.S.C. § 102(b) as being anticipated by Dattagupta et al.

The Examiner takes the position that Dattagupta et al disclose a conjugate comprising a polymeric carrier conjugated with multiple fluorescein molecules (i.e., both a marker and a hapten), wherein the monomeric units are nucleotides and a marker is specifically linked to the 3' end. The Examiner refers to example 1. Moreover, the Office Action states, the reference discloses the use of psoralen derivatives to photochemically label the DNA with either fluorescein, rhodamine or biotin, and psoralen is known to specifically react with pyrimidines, thereby specifically labelling those positions where a pyrimidine is located.

In applicants' Response of September 5, 1997, applicants argued that the invention is distinguishable from Dattagupta et al in that in the invention a non-statistical insertion of labelling groups and haptens at predetermined positions on the carrier is carried out, which is not disclosed in Dattagupta et al. Therefore, applicants argued that Dattagupta et al did not anticipate the claimed invention. However, in the present Office Action, the Examiner refers to the fact that psoralen is known to specifically react with

pyrimidines, and therefore psoralen would specifically label those positions where a pyrimidine is located.

Applicants submit that Dattagupta et al does not anticipate the present invention. In order to be a valid anticipatory reference, the identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ 2nd 1913, 1920 (Fed.Cir. 1989). It is error to ignore specific limitations of a

claimed invention which distinguish over a cited reference. *In re Glass*, 176 USPQ 49 (CCPA 1973). In the present case, the discussion of the use of psoralen derivatives is disclosed on column 5, lines 14-21 of Dattagupta et al. This disclosure merely describes how the labeled ligand is attached to the nucleic acid. Column 5, lines 6-10, disclose that the nucleic acid is covalently linked to a ligand by photochemical methods. Psoralen derivatives are used as the photoreactive agent for this covalent linkage. There is absolutely no disclosure of the use of psoralen derivatives to specifically label positions where a pyrimidine is located. Thus, because Dattagupta et al does not disclose the identical invention of the present case in as complete detail as is contained in the claim, the rejection under 35 U.S.C. § 102(b) is invalid, and should be withdrawn.

Psoralens form intercalation compounds with DNA. The formation of these compounds is a process which takes place on a purely statistical basis, wherein the pyrimidines of the DNA are labelled. Photochemical fixing, however, is very laborious and is not quantitative when only several labels are introduced (this is the procedure proposed by Dattagupta et al in column 5, lines 17-21). Even a defined and predictable incorporation of psoralens into DNA is not possible quantitatively. This becomes clear from the Spielmann et al reference, page 4516, right column, to the end of the first paragraph. A copy of this reference is attached to this Response for the Examiner's convenience. According to this reference, yields of only 36-80% are achieved in the case of photochemical labelling of an oligonucleotide octamer with psoralen. This means that many pyrimidine positions have not been labelled at all. Therefore, one cannot speak of a defined incorporation of labelling groups into DNA in the case of Dattagupta et al.

If a second label, such as fluorescein, is incorporated into the DNA octamer, again by statistic methods, a DNA is obtained which in addition to the statistically incorporated psoralens also contains randomly incorporated fluoresceins. If the number of monomeric units (in this case DNA octamers) was increased to 100, every monomeric unit of which is labelled statistically, a statistically labelled conjugate would be obtained. By no means would this product be a defined conjugate according to the present invention.

Regarding the site specificity of the incorporation of psoralens into pyrimidines, applicants also attach a publication by Gia et al, from which it emerges that the formation of (psoralen-induced) cyclobutane dimers takes place preferably in T-rich regions; however, the formation of covalent bonds with cytosines can be detected as well (see Fig. 3, page 4491). This makes it clear that the incorporation of psoralens at specific positions as proposed by Dattagupta et al takes place only at a certain percentage, and not in a defined and predictable manner (as with the present invention).

Dattagupta et al describe protein-nucleic acid conjugates, wherein the nucleic acid carries labelling groups such as psoralen and wherein the protein ("hapten") is always coupled to the 3'-end of the nucleic acid (carrier). As opposed to this, in the present invention, the selective build-up of carriers having correspondingly functionalized monomers has the advantage of labelling at specific positions which are not restricted to the 3'-end from the beginning. According to the invention, and contrary to Dattagupta et al, label and hapten can be incorporated flexibly, as far as their number and position are concerned. Therefore, applicants respectfully submit that the present invention is not anticipated by Dattagupta et al.

Claims 1-6, 11, 12, 15, 16, 27, 29 and 30 are rejected under 35 U.S.C. § 102(b) as being anticipated by Brederhorst et al. The Examiner takes the position that Brederhorst et al disclose a conjugate comprising a polymer of 21 amino acids which contains three haptens and one solid-phase binding group.

As applicants pointed out in the Response of September 5, 1997, Brederhorst et al does not anticipate the present invention, because the insertion of the haptens and the labelling groups in the reference does not occur at predetermined positions on the carrier, as required in the present claims. In Brederhorst et al, single monomeric derivatives are not derivatized during the chemical synthesis. The Examiner has not addressed applicants' arguments in the present Office Action. Applicants respectfully request that the Examiner specifically point out where he believes the present invention is anticipated by Brederhorst et al, or else remove this rejection.

Claims 21 and 23-26 are rejected under 35 U.S.C. § 102(b) as being anticipated by Smith et al. The Office Action states that Smith et al disclose the solid phase synthesis of oligonucleotides containing at predetermined positions monomers capable of further derivatization (i.e., with fluorescein, a hapten, binding group and marker group) through amino functional groups. The Office Action states that these functional groups are taught to be protected by a wide variety of protecting groups which are selectively removable under acidic or basic conditions. The synthesis of hapten-substituted oligonucleotide can be accomplished either co-synthetically or post-synthetically.

Applicants submit that Smith et al does not anticipate or render obvious the present invention.

Smith et al disclose a method of synthesizing oligonucleotides composed of monomeric units each of which contains a protected amino group. The protected amino group can be deprotected, and a detectable moiety can be attached thereto. See column 9, lines 16-21 and column 11, lines 27-32. Columns 29-33 disclose the synthesis of oligodeoxyribonucleotides containing a 5'-amino terminus. The amino group is protected by either Fmoc or MMT. Fmoc is a basic-labile amino protected group, while MMT is an acid-labile protecting group. The reaction scheme for such synthesis can be found on columns 31 and 32. This reaction scheme clearly discloses that oligonucleotides were either formed with Fmoc-protected amino groups **or** MMT-protected amino groups. Thus, there is no disclosure of an oligonucleotide containing **both** kinds of protecting groups, such as claimed in original claims 25 and 26 (which correspond to new claims 64 and 65).

Example 12, found on columns 35-38, discloses the conjugation of a dye to the 5'-amino terminus of the oligonucleotide. Column 37, line 9 through column 38, line 2 discloses that it is necessary to employ an acid-labile protecting group in order to conduct this reaction, because basic conditions may degrade the oligonucleotide. This is further evidence that the subject matter of original claims 25 and 26 is not disclosed in Smith et al.

Example 13, found on columns 38-42, discloses the conjugation of two different dyes (i.e., eosin-5-isothiocyanate and Texas Red) with an oligonucleotide. It is clear from the disclosure on column 40, lines 54-60, that the amino groups are merely **statistically reacted** with the dyes, and are **not** reacted at predetermined positions on the oligonucleotide. This section states that analysis of the conjugates indicated that the reaction "proceeded to about 80% completion" in the case of eosin-5-isothiocyanate, while

in the case of Texas Red, the reaction "proceeded to only about 20-30% completion." Thus, it is clear that the dyes were added statistically, and not at predetermined positions.

Similarly, in example 15, found on columns 50-52, conjugates containing the dye fluorescein-5-isothiocyanate was added in a statistical manner, and not at predetermined positions. Column 51, lines 51-53, disclose that in one experiment, the fluorescent product accounted for about 50% of the total amount of amino-containing DNA present in the sample. In another example, disclosed on column 51, lines 61-63, the fluorescent product accounted for at least 90% of the total amount of amino-containing DNA in the sample. Smith et al attribute the different results to the presence of the glycine moiety on the 2'-amino group of the sugar ring. Smith et al state that by reducing the steric hindrance, access by dye increases the amount of dye/DNA conjugate obtained.

It is clear that Smith et al do not disclose the synthesis of oligonucleotides containing marker groups at predetermined positions on the oligonucleotide. Therefore, it cannot be stated that Smith et al anticipates new claim 60, and the dependent claims thereon.

Claims 8 and 10 are again rejected under 35 U.S.C. § 103(a) as being unpatentable over Dattagupta et al in view of Bredehorst et al and further in view of Neilsen et al for reasons of record. In addition, claims 2 and 14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bredehorst et al in view of Gadow et al, for reasons made of record in the rejection of original claim 14 in the previous Office Action.

Claims 21, 23 and 24 are again rejected under 35 U.S.C. § 103(a) as being unpatentable over Smith et al, for reasons of record. Claims 27-30 are again rejected under 35 U.S.C. § 103(a) as being unpatentable over Bredehorst et al in view of Smith et

al for reasons of record. Claims 18-20 are again rejected under 35 U.S.C. § 103(a) as being unpatentable over Bredehorst in view of Berzofsky et al for reasons of record.

Claim 22 is newly rejected under 35 U.S.C. § 103(a) as being unpatentable over Smith et al in view of Buchardt et al. Smith et al has been discussed above. The Examiner concedes that Smith et al do not teach a peptide carrier synthesized from amino acid derivatives. The Examiner is relying on Buchardt et al to make up for this deficiency. Buchardt et al teach the production of peptide nucleic acids. These are considered to come within the "amino acid derivatives" of claim 22. The Examiner takes the position that it would have been *prima facie* obvious to a person having ordinary skill in the art at the time the invention was made to utilize PNA as a carrier molecule because of the stability found in this molecule.

Each of these rejections is based on a primary prior art reference discussed above (i.e., Dattagupta et al, Smith et al or Brederhorst et al). Therefore, applicants submit that none of these rejections is valid, since none of the primary references have anything to do with the present invention. Thus, the combination of these references with other documents and with each other, would not lead to the subject matter of the present claims.

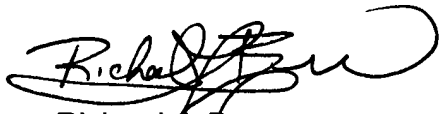
In view of the amendments and remarks above, applicants submit that this application is in condition for allowance and request reconsideration and favorable action thereon.

If for any reason, the Examiner feels the application is not now in condition for allowance, it is respectfully requested that the Examiner contact, by telephone, applicants' undersigned attorney at the indicated telephone number to arrange for an interview to expedite the disposition of this application.

In the event this paper is not timely filed, applicants hereby petition for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 14-1060, along with any other fees which may be required with respect to this application.

Respectfully submitted,

NIKAIDO, MARMELSTEIN, MURRAY & ORAM LLP



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